REMARKS

Status of the Claims

Claims 1-9 were pending. Claim 1 has been amended to incorporate the limitations of claim 8, which has been canceled without prejudice or disclaimer, and to specify that the sequences of the test polypeptide are randomly generated, as described for example on page 32, lines 1-3. In addition, claim 1 has been amended to specify that the DNA binding domain is a zinc finger, as described throughout the specification, for example on pages 32, line 31 to page 32, line 11 and pages 63-64, and that the zinc finger DNA binding domain and activation domain are heterologous, as described for example on page 28, lines 5-14. Claim 9 has been amended to depend from pending claim 1 rather than canceled claim 8. Finally, claim 2 has been amended to make it explicit that the transcriptional regulatory sequence includes at least one binding site for the DNA binding domain of the fusion protein described in (a) of claim 1. Thus, claims 1 to 7 and 9 are pending as shown above.

Interview Summary

Applicants greatly appreciate Examiner Shibuya's participation in a telephone conference on Friday April 8, 2005, during which draft claim amendments and the Menzel reference were discussed. Agreement was not reached during the interview, but Applicants thank Examiner Shibuya for his careful consideration of the amendments, suggestions regarding claim amendments (incorporated above) and particular passages of Menzel (addressed below).

Rejections Withdrawn

Applicants note with appreciation withdrawal of the previous rejections under 35 U.S.C. § 112, first and second paragraphs.

35 U.S.C. § 112, Second Paragraph

Claim 2 was rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for reciting the "DNA binding domain of (a)." Applicants have amended claim 2 as shown above to make it explicit that the DNA binding domain is of the fusion protein encoded by the chimeric gene of (a). Accordingly, the rejection has been obviated and can be withdrawn.

35 U.S.C. § 102

Claims 1, 3, 5 and 7 were rejected under 35 U.S.C. § 102(e) as allegedly anticipated by US Patent Publication 2003/0003449 (hereinafter "Menzel"). (Office Action, paragraph 9). Menzel is cited for teaching a method for selecting a dimerizing test polypeptide, as claimed. *Id.*

The foregoing amendments to claim 1 obviate the rejection because Menzel does not teach (1) libraries or randomly generated sequences encoding test polypeptides; (2) use of zinc finger DNA binding domains; (3) fusion proteins in which the DNA binding domain and activation domains are heterologous; and/or (4) selection of dimerizing peptides, namely peptides that link two fusion proteins together as a homodimer.

Applicants first note that the pending claims are drawn to methods for selecting peptides that promote homodimerization of two fusion proteins (each fusion protein comprising a DNA binding domain, activation domain and test polypeptide). In contrast, Menzel claims and describes methods of identifying tagged dominant-negative elements (TDNEs) that interfere with previously identified protein binding partners (*see, e.g.,* claim 1 of Menzel).

Thus, with regard to libraries, Menzel teaches either libraries of TDNEs that interfere with dimerization or libraries of "intentionally designed" sequences, namely fragments of polypeptides that have previously shown to be dimerizing peptides (see, e.g., paragraphs [0136] and [0257], emphasis added:

> According to the present invention, cDNA sequences from, e.g., new genes of interest, either complete or partial, may be fused to the DNA binding/activation domain of AraC. The dimerization capacity of the so generated chimeras may be tested by measuring their ability to activate transcription of an AraC-dependent promoter, preferably operably linked to a reporter gene (see Section 5.4.1, supra). **In those instances where activation is noted, libraries are generated which are composed of subfragments of the dimerizing sequences fused to a "carrier" protein, so that a TDNE library is generated.**
>
> ... Insertion of randomly fragmented gene segments, encoding subfragments of **the** dimerization polypeptide fused to the AraC-DNA binding domain, can restore the reading frame of the EGFP gene by translationally fusing such subfragment polypeptides to the EGFP gene.

In contrast, the claimed methods make use of library comprising a plurality of randomly generated sequences test polypeptides (claim 1) that allow for dimerization. As defined on page 32 of the specification randomly generated sequences do not have a predetermined sequence and

are unlike sequences that are known prior to synthesis. Thus, not only is Menzel's goal of finding TDNEs at cross-purposes with the claimed methods, Menzel's "libraries" are completely unlike the libraries of the pending claims.

Similarly, Menzel fails entirely to describe zinc finger DNA binding domains. Accordingly, Menzel cannot anticipate any of the pending claims.

In addition, Menzel's AraC system, on which the rejection was primarily based, is not a fusion of a zinc finger DNA-binding domain and heterologous activation domain. Rather, the DNA-binding domain and activation domain of AraC are "intimately associated." *See,* paragraph [0134]:

> The AraC protein, which comprises 292 amino acid residues, consists of three (3) functional AraC domains. Stoner and Schleif, 1982, J. Mol. Biol. 152:649-652. Residues one (1) through 170 are involved in the dimerization of AraC molecules and the binding of arabinose. A flexible linker domain, i.e., amino acid residues 171 thorough 178, links the dimerization domain to the DNA binding domain and is defined by amino acid residues 179 through 292. The **transcriptional activation function of the AraC protein is intimately associated with the DNA binding domain**.

Thus, in view of the foregoing, the rejection under 35 U.S.C. § 102 based on Menzel should be withdrawn.

35 U.S.C. § 103

Claims 1, 2 and 6 were rejected under 35 U.S.C. § 103 as allegedly obvious over Menzel in view of U.S. Patent No. 6,326,150 (hereinafter "Golemis"). (Office Action, paragraph 10). Menzel was cited as above and Golemis was cited for teaching an interaction trap assay system comprising a first and second reporter genes. *Id.* In addition, claim 1, 8 and 9, were rejected as allegedly obvious over Menzel in view of Jappelli et al. (Office Action, paragraph 11). Menzel was cited as above and Jappelli was cited for teaching methods of identifying dimerizing polypeptides using a homodimerization system in *E. coli* using libraries encoding random test polypeptides. *Id.*

For the reasons noted above, Menzel does not teach or suggest critical features of the pending claims, most notably, failing to teach or suggest methods of selecting peptides that mediate homodimerization of fusion proteins encoded by a library, as claimed. Thus, the

combination of Menzel and Golemis or Jappelli cannot render any of the pending claims unpatentable.

Applicants note again that Menzel is drawn to finding TDNEs that *inhibit* protein-protein interactions (see, claim 1 and paragraph [0109]):

> The above outlined approach, based on the system, therefore provides a microbe-based strategy to identify candidate TDNEs that will block protein-protein interactions of interest and thereby identify TDNEs that will act as dominant-negative sequences. The disruption of the native tertiary structure of a cognate parental protein by a dominant-negative element is expected to lead to the ablation of function. Ablation of function will allow for a test of a hypothesized function. Moreover, ablation of function may lead to the discovery of a protein's function even in the absence of a hypothesis. In addition to providing a chimera that can assess function in model systems, inhibitory TDNEs identified with this system may also have value as a therapeutic agent in those cases where the ablation of function has a desirable therapeutic endpoint.

Moreover, with respect to identifying protein-protein interactions, Menzel teaches systems that identify known binding partners (*see, e.g.,* paragraphs [0049] and [0052] [emphasis added):

> Two primary types of schemes are possible. Such a system could be used to identify or "trap" an interaction between a partner protein and a truncated fragment, fused to the appropriate carrier, **derived from a protein previously shown to interact**. The isolation of interacting partners in a library of chimera identifies members that define constituent interacting peptides. These chimera identify those members most likely to act as dominant-negative elements; interaction is a prerequisite of a dominant-negative element. A second type of approach will involve "blocking" an existing interaction. Such existing interactions can be based on interactions defined in a microbial, e.g., yeast or bacterial, based interaction system. Chimera defined by their "blocking" properties will have a high probability of being dominant-negative elements in that the ability to block a protein-protein interaction of the target protein, or fragment thereof, **will already have been shown**. The above approaches also provide a means of assuring that in-frame clones have been identified. Only one out of six inserts of randomly generated, e.g., sheared fragments will be correct: one half will have the correct orientation and one third of these will have the correct reading frame. The identification of a "blocking" or "trap" fragment will, therefore, prescreen a library for correctly oriented and in-frame members that have already demonstrated protein-protein interaction properties with the target or particular protein of interest.
>
> As stated above, the targeted interaction is known to define an interaction **that has been demonstrated**, as part of a systematic procedure, to be vital to the

> function of the protein of interest. Further, the procedures used to define dominant-negative chimera can define a minimal interacting peptide that will cover a minimal interacting surface.

Furthermore, as acknowledged by the Examiner and for the reasons noted above, Menzel teaches nothing about libraries of chimeric genes (including randomly generated sequences encoding test dimerizing polypeptides) as claimed. (Office Action, paragraph bridging pages 12-13). At best, Menzel teaches making libraries of fragments of the **previously identified** dimerizing polypeptides.

Given that Menzel teaches nothing about libraries as claimed and is drawn to methods of selecting TDNEs that block known protein-protein interactions, Applicants submit that there is no combination of Menzel and Golemis or Jappelli that would result in the claimed methods. Indeed, combining Menzel with Jappelli would result in an entirely different method, namely one in which peptides that **inhibit** dimerization of **known** protein partners are selected.

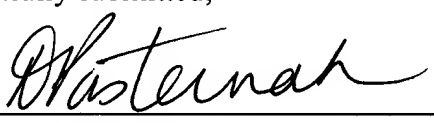
Accordingly, Applicants submit that a *prima facie* case of obviousness has not (and indeed cannot) be based on Menzel. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing remarks, Applicants submit that all pending claims are in condition for allowance and request early notification to that effect. Should the Examiner have any further questions, he is invited to contact the undersigned.

Respectfully submitted,

Date: April 13, 2005

By: 

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